Time-Varying Risk Factors for Long-Term Mortality After Coronary Artery Bypass Graft Surgery

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Background. **There is a substantial literature on short-term mortality risk factors for coronary artery bypass graft (CABG) surgery. However, very few studies have examined risk factors for long-term mortality.**

Methods. **We analyzed 56,543 veterans who underwent CABG surgery at one of 43 VA cardiac surgery centers between October 1, 1991, and March 30, 2001. Each patient was followed for a minimum of 3.5 months and a maximum of 9.5 years for mortality assessment. The time-varying effects of 22 mortality preoperative risk factors were evaluated using both standard Cox regression models and Cox B-spline regression models.**

Results. **Six variables showed significant varying effects over time on mortality after surgery. The effects of previous heart surgery or preoperative intra-aortic balloon pump carried about 5 times and 3 times the risk, respectively, of dying on the first day after surgery, but were not significant during long-term follow-up. Conversely, diabetes had little additional risk immediately after surgery, but the risk increased steadily and doubled at 9.5 years after surgery. Three other risk variables—age, chronic obstructive pulmonary disease, and urgent or emergent status—also had risk changing by 50% to 60% over the next decade. Most of the other 16 risk variables were significantly associated with mortality, but the risk did not vary substantially over time.**

Conclusions. **Risk associated with some preoperative variables can change significantly during the decade after surgery, and risk assessments that assume constant risk during the postoperative period may substantially overestimate or underestimate risk at some times. These findings may help clinicians identify appropriate management strategies for patients during the years after CABG surgery, and support an emphasis on noncardiac comorbidities during later postoperative periods.**

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Preoperative risk factors for short-term (≤ 30 days), intermediate-term (31 to 210 days), and long-term (>210 days) mortality after coronary artery bypass graft (CABG) surgery have been investigated [1–7], and differences in risk factor sets for these time periods have been noted [7]. However, the majority of previous studies have focused on risk factors for short-term outcomes, and little is known about risk factors for long-term mortality or how these risk factors may vary over time. Time-varying risk means that a given preoperative risk factor may be associated with different degrees of risk at different times after surgery. We have previously shown that effects of risk variables can vary in the 7 months after surgery, such that some cardiac risk factors (eg, prior myocardial infarction) confer maximal risk perioperatively whereas some noncardiac risk variables (eg, chronic obstructive pulmonary disease) have increasing impact over the months after the operation.

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The goal of the present study was to examine the time-varying effects of preoperative risk variables on long-term mortality in a large cohort of CABG surgery patients, and to compare the results with previous investigations of shorter-term risk factors. It is hoped that the results of this study will help inform better preoperative risk stratification and counseling of patients with regard to mortality risk during the decade after the operation.

Patients and Methods

Study Population

The VA Continuous Improvement in Cardiac Surgery Program (CICSP) has collected risk and outcome data on all subjects undergoing cardiac surgery at the 43 VA cardiac surgical centers since 1987 [1, 2]. All VA patients who underwent CABG surgery at a VA cardiac surgery center between October 1, 1991, and March 30, 2001, were included in this study. For patients who had more than one surgery during this time period, only the last surgery was considered for analysis. Fifteen patients (0.03%) were omitted owing to missing patient identification information, 110 patients (0.2%) were removed because of irreconcilable

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problems with death dates, and 2 patients (0.004%) were omitted because of missing procedural information, giving a total study population of 56,543 patients.

Outcomes

The purpose of this study was to examine variation in risk factors over time for long-term survival of patients after CABG surgery. The outcome was all-cause mortality between the date of surgery and July 17, 2001, the closing date for records from the VA Beneficiary Identification and Record Locator System (BIRLS). Mortality assessments were made using both BIRLS and individual follow-up by VA personnel (including information from electronic medical records, cardiology clinics, and personal contact by CICSP surgical clinical nurse reviewers). The BIRLS, which has been shown to be comparable with the National Death Index for mortality assessment in a VA population [9], was used for the primary determination of mortality outcomes. Individual follow-up by CICSP personnel was used for confirmation and determination of any deaths missed by BIRLS.

Risk Variables

We considered 22 preoperative risk variables that have been previously established as mortality risk factors for CABG surgery [3, 6]. These 22 variables were categorized as either demographic or noncardiac, or cardiac by CICSP. The demographic or noncardiac variables considered were age, sex, body surface area (m^2), partially or totally dependent functional status, chronic obstructive pulmonary disease (COPD), peripheral vascular disease, cerebral vascular disease, current smoker, diabetes, and serum creatinine level of 1.5 mg/dL or greater. The cardiac risk variables considered were prior heart surgery, Canadian Cardiovascular Society (CCS) anginal class III or IV, prior myocardial infarction (regardless of time of occurrence), preoperative intra-aortic balloon pump (IABP), intravenous nitroglycerin 48 hours or less before operation, percutaneous transluminal coronary angiography (PTCA) 0 to 72 hours before surgery, ST-segment depression on preoperative electrocardiogram, New York Heart Association (NYHA) functional class III or IV, urgent or emergent surgical priority, number of stenotic coronary arteries 2 or more, left main coronary artery stenosis greater than 50%, and left ventricular ejection fraction less than 0.55.

Missing values of risk variables were imputed using the median for continuous variables or the most frequent category for categorical variables. Eighteen variables had less than 0.05% missing values, serum creatinine had 0.29% missing, number of stenotic coronary arteries and left main coronary artery stenosis (50% or more) had 2.5% and 2.4% missing, respectively, and left ventricular ejection fraction had 5.77% missing.

Statistical Analyses

Two separate multivariable methods were implemented to determine the independent time-varying effect of each risk variable. First, standard Cox proportional hazards survival analysis was used to estimate for each risk variable a constant hazard ratio (ie, the same risk applies over time after surgery) [10]. The hazard ratio represents the increased risk for a patient with the risk factor compared with a patient without the risk factor, controlling for other variables in the model.

Second, Cox proportional hazards regression with the incorporation of linear B-spline functions of survival time after surgery was used to estimate possibly different hazard ratios at each day after surgery. The splines we used are functions composed of straight lines (first-order splines) that join and may change slope at prespecified times (knots, which we located at approximately the 10th, 25th, 50th, 75th, and 90th percentiles of death times, which correspond to 7, 98, 784, 1,645, and 2,324 days after surgery, respectively). These piecewise linear functions are capable of representing a wide variety of risk patterns over time, and provide one approach to modeling nonproportionality of risk (ie, varying risk over time) when necessary [11–14]. Comparison of the B-spline models with standard Cox regression indicates whether the risk varies with time after surgery.

A sequence of steps was used to determine whether each of the 22 risk factors had a significant and substantially time-varying association, and if so, to estimate the postoperative pattern of risk while adjusting for the remaining risk factors. That involved selecting the number and location of knots in the spline function for each risk variable while adjusting for other variables in time-constant form, comparing this spline function with a time-constant hazard function, and repeating the estimation and comparison with constant hazard while adjusting for other variables in their time-varying hazard form. We used both statistical criteria (likelihood ratio tests and the Bayesian information criterion [BIC] [15]) and clinical criteria (requiring that the hazard ratio vary by at least 50% over the 9.5-year follow-up) in determining risk variables that displayed time-varying risk. Details of statistical methods are given in the Appendix.

For each risk variable found to have time-varying hazard ratio, a graph of the hazard ratio and 95% confidence interval (CI) at each day after surgery is given. For risk variables with constant hazard ratio, an estimated hazard ratio, 95% CU, and p value are given. All statistical analyses were conducted using PROC PHREG in SAS version 8 (SAS Institute, Cary, North Carolina), and sample code is available upon request to the corresponding author.

Results

Baseline Patient Characteristics

Baseline patient characteristics for the 22 preoperative risk variables considered in this study are shown in Table 1. The average age of the study population was 63 years. A sizeable proportion of patients had noncardiac comorbidities such as diabetes (31.4%), COPD (23.3%), and peripheral vascular disease (23.0%). More than half of the

Table 1. Characteristics of the Study Population (N = 56,543)

Variable	Percent or Mean (SD)
Demographic/noncardiac	
Age (years)	63 (9)
Male sex	99.1%
Body surface area (m^2)	2.0 (0.2)
Partially or totally dependent functional status	14.1%
Chronic obstructive pulmonary disease	23.3%
Peripheral vascular disease	23.0%
Cerebral vascular disease	19.7%
Current smoker	31.4%
Diabetes mellitus	30.6%
Serum creatinine level ≥ 1.5 mg/dL	16.8%
Cardiac	
Prior heart surgery	8.4%
CCS anginal class III or IV	78.6%
Prior myocardial infarction	58.5%
Preoperative intra-aortic balloon pump	5.4%
Intravenous Nitroglycerin ≤ 48 hours before surgery	16.1%
PTCA 0–72 hours before surgery	2.2%
Preoperative ST-segment depression on electrocardiogram	22.0%
NYHA functional class III or IV	14.9%
Urgent or emergent surgical priority	19.1%
Number of stenotic coronary arteries ≥ 2	92.7%
Left main coronary artery stenosis > 50%	27.9%
Left ventricular ejection fraction < 0.55	48.4%

NYHA = New York Heart Association; CCS = Canadian Cardiovascular Society; PTCA = percutaneous transluminal coronary artery angioplasty.

patients had a prior myocardial infarction (58.5%) and nearly half (48.4%) had a reduced left ventricular ejection fraction (<0.55). Prior heart surgery had been performed on 8.4% of the patients, and 5.4% of the patients received a preoperative IABP.

Outcome

The cumulative survival curve for the study population is shown in Figure 1. The curve appears to level off several months after surgery, perhaps indicating the end of the acute recovery phase. Percents of patients surviving 30 days, 6 months, 1 year, 3 years, 5 years, and 9.5 years after surgery were 96.5%, 94.8%, 92.3%, 87.0%, 81.0%, and 66.0%, respectively.

Time-Varying Risk Factors

When all risk variables were entered in the forms (spline or constant) chosen by the variable selection methods described in the Appendix, six of the 22 risk variables were found by statistical and clinical criteria to have a time-varying association with mortality, namely, age, COPD, diabetes, prior heart surgery, preoperative IABP, and urgent or emergent surgical priority. For these six

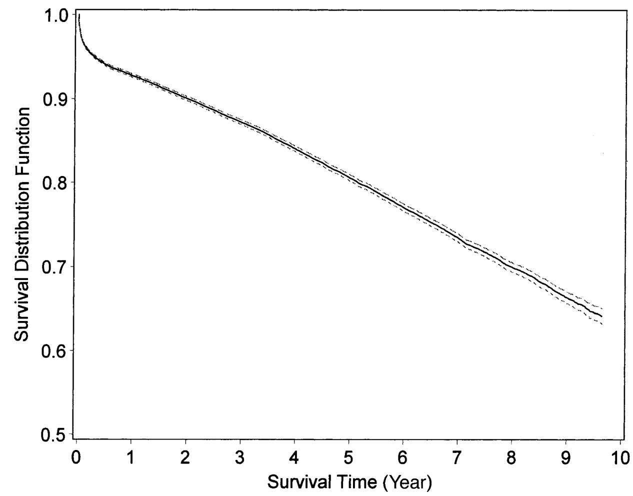

Fig 1. Kaplan-Meier survival curve (solid line) and 95% confidence limits (dashed lines) after coronary artery bypass graft surgery.

variables, Table 2 shows the statistical measure, BIC, of how much better the time-varying model fits the data compared with the time-constant model, and the clinical measure (variation in hazard ratio over the follow-up period) showing the magnitude of variation in risk during the follow-up period. Prior heart surgery showed the greatest magnitude of hazard ratio variation, with preoperative IABP and diabetes also showing substantial variation in hazard ratio over time.

Figures 2 through 7 show the estimated hazard ratios and confidence bands as functions of time for the six

Table 2. Summary for Risk Predictors Estimated to Have Time-Varying Hazards[a]

Risk Factor	BIC Difference[b]	Change in Hazard Ratio[c]
Demographic/noncardiac		
Age (per 10 years)	33.3	1.52
Chronic obstructive pulmonary disease	24.0	1.62
Diabetes mellitus	69.2	2.62
Cardiac		
Prior heart surgery	174.4	5.05
Preoperative intra-aortic balloon pump	36.1	3.68
Urgent and emergent surgical priority	14.0	1.62

[a] These Models Are Graphed in Figures 2–7. [b] The BIC difference is the difference in the BIC values for two multivariate models. Each model contained all risk factors in the form (time-varying or time-constant) chosen by model selection. They differed in whether the risk factor being examined was in time-constant or time-varying form. A large difference in BIC indicates a greater improvement from the time-varying hazard ratio compared to the time-constant hazard ratio for the risk factor being examined. [c] The change in hazard ratio is the ratio of largest to smallest hazard ratio values of the risk factor over the study period, and indicates the magnitude of variation in the hazard ratio over time.

BIC = Bayesian information criterion.

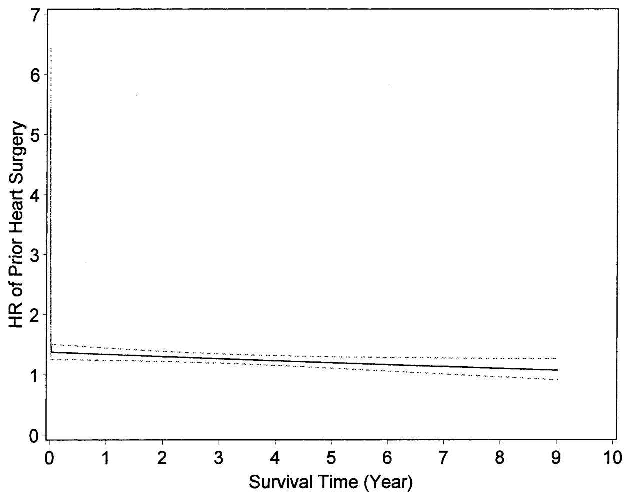

Fig 2. Hazard ratio (HR [solid line]) and 95% point-wise confidence bands (dashed lines) for risk factor prior heart surgery at each day after coronary artery bypass graft surgery. A horizontal line at 1 would indicate no increased risk.

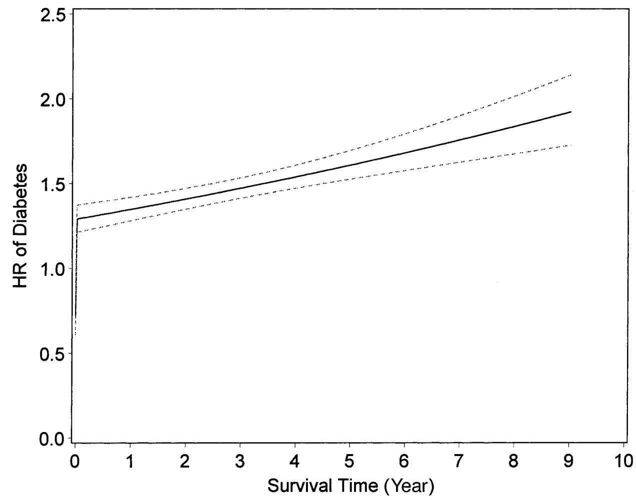

Fig 4. Hazard ratio (HR [solid line]) and 95% point-wise confidence bands (dashed lines) for risk factor diabetes at each day after coronary artery bypass graft surgery. A horizontal line at 1 would indicate no increased risk.

variables estimated to have time-varying risk. The hazard ratio for prior heart surgery, after adjusting for other covariates (Fig 2), was 5.43 (95% CI: 4.58 to 6.42) on the day of surgery, but rapidly decreased to 1.38 (95% CI: 1.25 to 1.51) by 7 days after the operation. The hazard ratio for preoperative IABP (Fig 3) was 2.99 (95% CI: 2.62 to 3.40) on the day of surgery and decreased steadily to 1.28 (95% CI: 1.12 to 1.48) by 3 to 4 months after surgery. Further slight decreases in risk are noted for both prior heart surgery and preoperative IABP during the remainder of the 9.5-year period. The hazard ratio for diabetes (Fig 4) was not significant immediately after surgery but quickly increased to 1.29 (95% CI: 1.12 to 1.48) at 1 week after surgery. The hazard ratio continued to increase over time, to 1.92 (95% CI: 1.73 to 2.14) by the end of the study period.

Three other risk variables (age, COPD, and urgent or emergent surgical priority) had time-varying hazard ratios, though the time variation was substantially less than for prior heart surgery, preoperative IABP, and diabetes. Figures 5 through 7 show the estimated hazard ratios and confidence bands as functions of time for these three variables. Maximum hazard ratios were about 50% to 60% greater than minimum hazard ratios for these variables. The hazard ratio for age per 10 years was 1.08 (95% CI: 0.98 to 1.18) on the day of surgery, increased to a maximum hazard ratio of 1.66

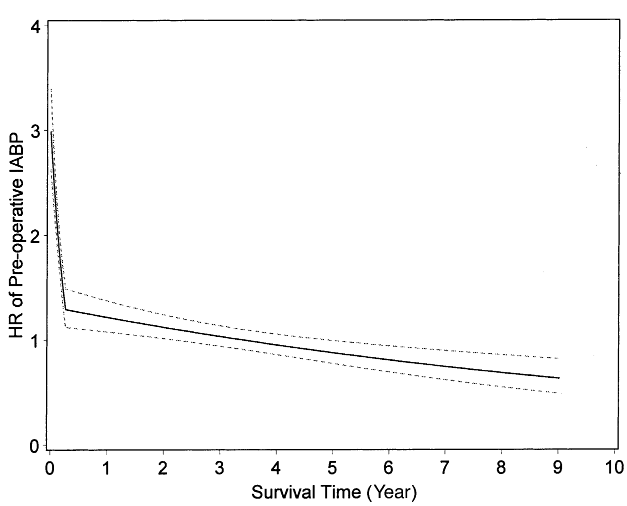

Fig 3. Hazard ratio (HR [solid line]) and 95% point-wise confidence bands (dashed lines) for risk factor preoperative intra-aortic balloon pump (IABP) at each day after coronary artery bypass graft surgery. A horizontal line at 1 would indicate no increased risk.

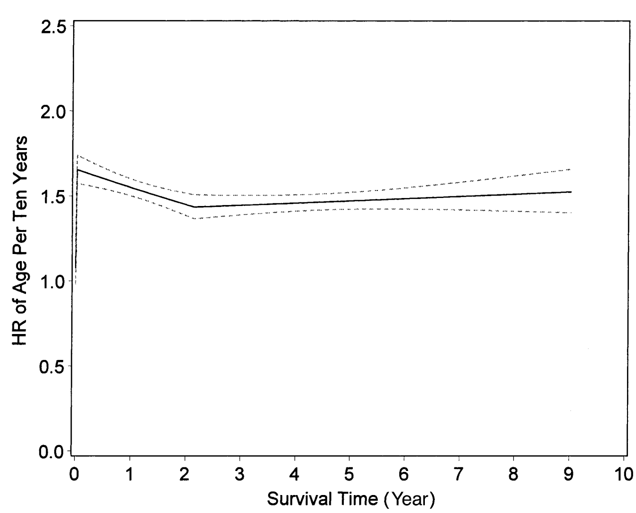

Fig 5. Hazard ratio (HR [solid line]) and 95% point-wise confidence bands (dashed lines) for predictor age per 10 years at each day after coronary artery bypass graft surgery. A horizontal line at 1 would indicate no increased risk.

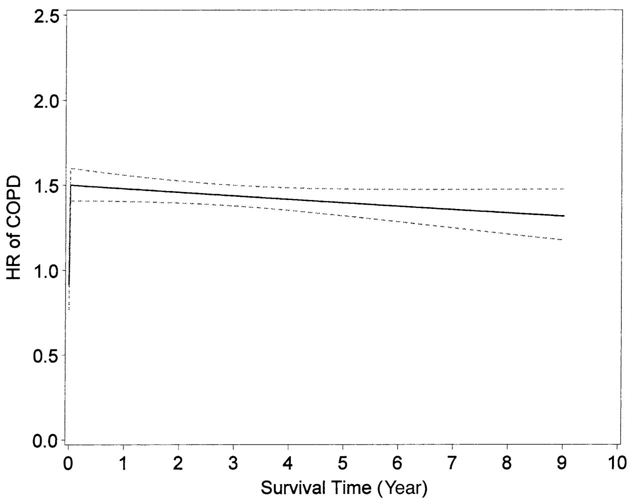

Fig 6. Hazard ratio (HR [solid line]) and 95% point-wise confidence bands (dashed lines) for predictor chronic obstructive pulmonary disease (COPD) at each day after CABG surgery. A horizontal line at 1 would indicate no increased risk.

(95% CI: 1.57 to 1.74) by 7 days after surgery, and then decreased or leveled off at a hazard ratio approximately 1.4 to 1.6 per 10 years of age. The hazard ratio for COPD was 0.94 (95% CI: 0.79 to 1.13) on the day of surgery, increased to 1.52 (95% CI: 1.43 to 1.62) by 7 days after surgery, then gradually decreased to around 1.3. The hazard ratio for urgent and emergent surgical priority was 1.59 (95% CI: 1.42 to 1.78) on the day of surgery and quickly decreased to 1.02 (95% CI: 0.94 to 1.11) by 10 weeks after surgery.

Time-Constant Risk Factors

Of the remaining 16 variables for which we estimated time-constant hazard ratios, 14 had hazard ratios significantly different from 1 (PTCA 0 to 72 hours before surgery and CCS anginal class III or IV were not significant). These estimates were obtained from the models in which all variables were in the forms (either time-constant or time-varying) chosen by model selection. These 16 variables, with their overall hazard ratios and 95% CI for the 9.5-year period after CABG surgery are listed in Table 3. Only serum creatinine level 1.5 mg/dL or greater had estimated constant hazard ratio greater than 1.5 (1.70, 95% CI: 1.63 to 1.77, $p < 0.0001$) over the 9.5-year period.

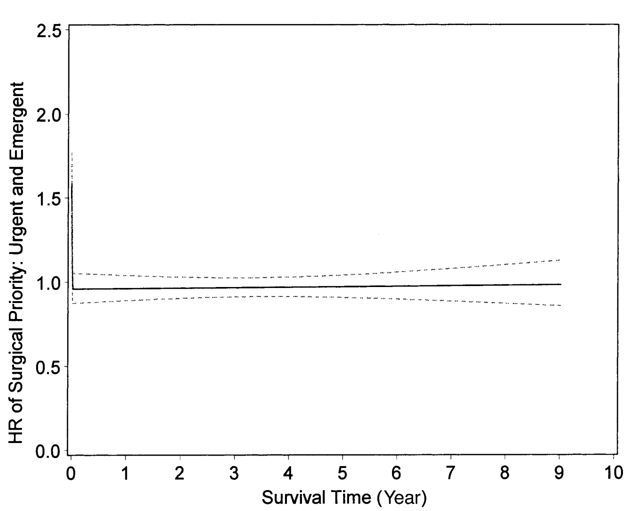

Fig 7. Hazard ratio (HR [solid line]) and 95% point-wise confidence bands (dashed lines) for predictor urgent or emergent surgical priority at each day after CABG surgery. A horizontal line at 1 would indicate no increased risk.

Table 3. Hazard Ratios (95% Confidence Intervals [CI]), and p Values for Risk Predictors Estimated to Have Time-Constant Hazards

Variable	Hazard Ratio (95% CI)[a]	*p* Value
Demographic/noncardiac		
Male sex	0.79 (0.64, 0.99)	0.042
Body surface area (m^2)[b]	1.37 (1.23, 1.52)	<0.0001
Partially or totally dependent functional status	1.19 (1.13, 1.25)	<0.0001
Peripheral vascular disease	1.36 (1.30, 1.42)	<0.0001
Cerebral vascular disease	1.29 (1.24, 1.35)	<0.0001
Current smoker	1.29 (1.23, 133)	<0.0001
Serum creatinine level ≥ 1.5 mg/dL	1.70 (1.63, 1.77)	<0.0001
Cardiac		
CCS anginal class III or IV	0.98 (0.93, 1.02)	0.320
Prior myocardial infarction	1.16 (1.11, 1.21)	<0.0001
Intravenous nitroglycerin ≤ 48 hours before surgery	1.06 (1.01, 1.12)	0.028
PTCA 0–72 hours before surgery	0.96 (0.85, 1.09)	0.53
Preoperative ST-segment depression on electrocardiogram	1.05 (1.01, 1.10)	0.02
NYHA functional class III or IV	1.41 (1.35, 1.48)	<0.0001
Number of stenotic coronary arteries ≥ 2	1.08 (1.00, 1.18)	0.047
Left main coronary artery stenosis ≥ 50%	1.11 (1.07, 1.16)	<0.0001
Left ventricular ejection fraction ≤0.54	1.33 (1.28, 1.38)	<0.0001

[a] Hazard ratio is adjusted for the effects of the other 21 covariates in their appropriate forms of either time-varying or time-constant. [b] Body surface area was included in model as $(\text{body surface area})^{-1}$.

CCS = Canadian Cardiovascular Society; NYHA = New York Heart Association; PTCA = percutaneous transluminal coronary artery angioplasty.

Comment

The purpose of this study was to estimate associations of preoperative risk variables with all-cause mortality over 9.5 years after CABG surgery, and to assess how the magnitude of risk from these variables changes over time after surgery. We examined 22 risk variables using statistical methods designed to estimate a different risk (hazard ratio) at each day after surgery. We noted significant and substantial time variation in the association of mortality with six of the risk variables, with some risk effects changing twofold or more over the 9.5-year period.

Three cardiac-related variables—prior heart surgery, preoperative IABP, and urgent or emergent surgical priority—were associated with high risk immediately after surgery but with subsequent rapidly decreasing risk over time. In all cases, these risks decreased or disappeared over the succeeding weeks or months. Comparing these results to estimated hazard ratios assuming the same risk at all times after surgery shows that the standard time-constant estimates substantially underestimate risk immediately after surgery and overestimate risk over the longer term. Thus, these three cardiac risk variables are even more important than previously often thought during the perioperative period, but appear to add little information toward predicting risk over the long term.

Three noncardiac variables—diabetes, age, and COPD—showed little risk immediately after surgery, but the risk increased rapidly during the weeks or months after surgery. In particular, the hazard ratio for diabetes continued to increase over long-term follow-up. These results indicate that assuming constant hazard ratio during the entire decade after surgery will overestimate risk immediately after surgery and underestimate risk over the long term. Finally, of the 16 risk variables for which we did not find substantially time-varying risk, 14 were associated with independent time-constant risk over the 9.5-year period after surgery. The highest time-constant independent risk was elevated serum creatinine. Of note, the risk from renal dysfunction was independent of the risk from diabetes, and, conversely, the time-varying risk from diabetes was independent of the constant risk from elevated serum creatinine.

Taken together, the results of this study emphasize that while cardiac factors are critical with regard to mortality risk in the early postoperative period, there is a clear shift toward noncardiac risk factors with regard to longer-term survival. Patients are often labeled as "cardiac patients" after CABG surgery, with emphasis on cardiac condition for extended periods of time. Yet, after the early recovery period it appears that emphasis on management of comorbid conditions, like diabetes and COPD, is critical toward longer-term survival. This underscores the importance of the "hand-off," or transition, from cardiothoracic surgery and cardiology back to primary care in the months after the operation. Future studies should evaluate whether disease management interventions for key comorbid conditions in post-CABG patients can improve outcomes. In addition, studies such as the evaluation of tight glycemic control in diabetics and smoking cessation interventions to reduce risk from COPD among post-CABG patients may be warranted to see if such interventions can improve long-term survival.

The general patterns of risk found in this study were consistent with previous investigations by our group focused in the first 7 months after CABG surgery [7, 8]. In those previous studies, we found that cardiac-related risks tended to be higher during the first weeks or month after surgery, and the effects of noncardiac factors appeared during the subsequent 6 months. The present study extends those results to much longer-term follow-up, uses a larger sample, and considers a more extensive set of preoperative risk variables.

The previous literature on risk factors for long term survival after CABG surgery is limited. Risum and colleagues [4] followed 1,025 patients for up to 10 years after CABG surgery and found previous heart surgery to be a strong independent predictor of early (≤ 30 days) but not of total mortality (as long as 10 years), consistent with our findings. In contrast, diabetes mellitus was not an independent predictor of either early or total mortality in that study. Srinivasan and coworkers [17] followed 840 elderly patients for as long as 5 years after CABG or valve surgery. Renal disease was the strongest independent predictor of mortality, but prior heart surgery and diabetes were not independent risk factors. Our study had over 50 times as many patients as either of these previous studies, and therefore had significantly higher power to assess risk effects such as the impact of diabetes on long-term mortality. Consistent with our study, Leavitt and coworkers [18] noted significant long-term risk associated with diabetes and even greater risk for diabetic subjects with renal failure, peripheral vascular disease, or both in 10-year follow-up of the large (36,641 patients) Northern New England Cardiovascular Disease database.

This study has several potential limitations. The VA population is largely male, and has a typically greater burden of comorbidities than other populations, so care is needed in generalizing our results to non-VA populations. Also, we did not have information on cause of death, and noted minor differences in mortality rates between the two methods we used to capture mortality (individual follow-up by VA personnel and BIRLS). However, previous sensitivity analyses (eg, Gao and associates [8]) indicated that these differences are not large enough to change results substantively. We also note that our results are specifically for patients after CABG surgery and may not necessarily apply with other types of cardiac surgery. For example, our group has previously noted substantial differences between post-CABG patients and post–valve replacement patients in effects of some risk variables on short-term (30-day) mortality [19].

In conclusion, we found that during the nearly 10 years after CABG surgery, the risk of death associated with several preoperative risk variables changed substantially. Risks from several cardiac risk variables were high immediately after surgery but dissipated quickly, whereas risks from several noncardiac-related variables increased over time after the operation. Our results suggest that after the immediate recovery from CABG surgery, a focus on noncardiac conditions may be most important to maximize long-term survival.

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Appendix

The Cox regression models with B-spline functions were estimated using SAS PROC PHREG, with time-varying covariates used to incorporate the spline functions of survival time [11–14]. We considered all spline functions with up to three knots, located at any of the five potential locations. Models selected in this study contained at most two knots, always located among the first three locations. In general, the results of these types of more complex Cox spline regression modeling approaches have been noted not to be very sensitive to the exact location of the B-spline knots [12]. We carried out several sensitivity studies of effects of knot location and also experienced this nonsensitivity.

As a statistical criterion for determining which models fitted our data best, we used likelihood ratio tests and the Bayesian information criterion (BIC) [15]. Likelihood ratio tests determine whether the hazard ratio varies statistically significantly with time after surgery. In models with each variable individually in time-varying spline form and adjusting for all other risk variables in time-constant form, all risk variables were found to have significantly time-varying hazard ratio ($p < 0.01$). However, this is a common occurrence in studies such as this with vary large sample sizes and power to detect very small deviations from null hypotheses, and when hazard ratio functions were examined the magnitude of variation in the hazard ratio over time was often very small and the hazard ratio took a complex form and was not of practical interest. Therefore, BIC values were also examined. The BIC takes into account how well the model predicts survival as well as how many parameters were estimated. A smaller BIC value indicates a model that has a higher probability of being correct for the given data. Kass and Raftery [16] discuss these issues and provide guidelines for how differences in BIC values between two models correspond to strength of evidence in favor of one of the models. We have used their criterion of a difference in BIC values greater than 10 corresponding to "very strong evidence." In our study, if a more complex model had BIC more than 10 units better than a simpler model, the more complex model was chosen, otherwise the simpler model was used. When we repeated analyses with different values, in some cases different numbers of variables were flagged as having time-varying hazard ratio, but the same several risk variables reported in the Results emerged as having the greatest degree of time variation. To ensure that variables with time-varying risk as determined by statistical methods also showed sufficient magnitude of variation over time to be of clinical interest, we also required that the highest estimated hazard ratio over the 9.5-year follow-up be at least 50% greater than the smallest estimated hazard ratio.